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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,741	01/23/2006	Yolande Chvatchko	ARS120	2192

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,741	CHVATCHKO, YOLANDE	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-42 and 44* is/are pending in the application.

4a) Of the above claim(s) *27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-26, 28-42 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 24-42 and 44 are pending.

2. Applicant's election without traverse of Group I, claims 24-42 (now claims 24-42 and 44) directed to a method of treating inflammatory and/or autoimmune diseases comprising the administration of a composition comprising a soluble protein comprising a sequence having at least 85% of homology with the mature form of the extracellular domain of human CD164 (SEQ ID NO: 1) and SEQ ID NO: 1 and multiple sclerosis as the species filed on 8/27/07, is acknowledged.

3. Claim 27 (non-elected species) is withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

3. Claims 24-26, 28-42 and 44 are under examination as they read on a method of treating inflammatory and/or autoimmune diseases comprising the administration of a composition comprising a soluble protein comprising a sequence having at least 85% of homology with the mature form of the extracellular domain of human CD164 (SEQ ID NO: 1) and SEQ ID NO: 1 and multiple sclerosis as the species.

4. Applicant's IDS, filed 8/31/06, is acknowledged.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 24-26, 28-42 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of inhibiting the proliferation of MBP specific T cells induced by AC1-11 comprising contacting said cells with soluble CD164 polypeptide, does not reasonably provide enablement for a method of treating any "inflammatory and/or autoimmune diseases" comprising the administration of a composition comprising a soluble protein comprising sequence having at least "85% of homology with the mature form of the extracellular domain of human CD164 (SEQ ID NO:1)" in claim 24, wherein said soluble protein is an "active mutein or an isoform of SEQ ID NO: 1" in claim 26, wherein said soluble protein is an "active derivative, a proteolysis-resistant modified form, a conjugate, a complex, a traction, a precursor, and/or a salt" in claim 39, wherein said inflammatory and/or autoimmune disease is multiple sclerosis in claims 40 and 44, or a method of inhibiting the expression of one or more cytokines in an individual comprising administering to said individual a composition comprising a soluble protein comprising a sequence having "at least 85% of homology with the mature form of the extracellular domain of human CD 164 (SEQ ID NO: 1)" in claim 41, wherein said cytokine is TNF-α, IFN-γ, IL,-2, IL-4, II,-5, or IL-10. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

One cannot extrapolate the teachings of the specification to the scope of the claims because the method claims are drawn to a method of treating inflammatory and/or autoimmune diseases such as multiple sclerosis with sCD164. The specification on page 68, under Example 5 discloses MBP-specific T cells were obtained from a commonly used model of pre-stimulated mature T cells in EAE. The specification on page 59, lines 3-5 discloses that sf-CD164 significantly inhibited the proliferation of MBP specific T cells induced by AC1-11. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. No animal model system is used to treat inflammatory and/or autoimmune diseases such as MS. Since the method of treating MS indices of administering to the animal an sCD164 can be species- and model-dependent, it is not clear that reliance on the a cell-based assay accurately reflects the relative human efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively treat any inflammatory and/or autoimmune diseases including MS or reach any therapeutic endpoint in humans by administering the sCD164. The specification does not teach how to extrapolate data obtained from in a cell-based assays to the development of effective in vivo mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Wiendl et al (Biodrugs 2002:16(3):183-200) teaches that a clinical study with BAY 36-1677 in patients with MS failed to show the desired pharmacological effects. Because of potentially superimposed immunological effects, the *in vitro* selectivity of BAY 36-1677 did not translate into clinical advantage (see p. 191, 2nd col., 1st full ¶). Further, Wiendl et al teach that despite rational therapeutic concepts, convincing preliminary animal experiments or positive experiences with other autoimmune diseases, some initial studies showed no proof of efficacy or failed because of unforeseen adverse effects in MS (see Table II, and Page 184, 2nd col.). Table II on page 187 of Wiendl et al shows that TCR-directed therapies either has no clinical effect or provided mixed clinical effect due to small number of patients, complexity and diversity of human autoimmune T cells, role of MBP in MS pathogenesis, heterogeneity and individuality of TCR-repertoire and antigen-specificity, among others. Wiendl et al teach that blockage of TNFα, a putative "key cytokine" in MS, failed in two trials (see section 2.1.3 on page 189). Further, in TNF-deficient mice, myelin-specific T cell reactivity fails to regress and the expansion of activated/memory T cells is abnormally prolonged, leading to exacerbated EAE (see page 190, 1st col., 2nd full ¶). In addition, `t Hart et al in (DDT 9(12):517-524, 2004) teach that while the animal model of choice

for MS is EAE, the effectivity in EAE models clearly does not predict effectivity in MS (see page 522, 2nd col., 1st ¶). Therefore, it is not clear that the skilled artisan could predict the efficacy of the sCD164 exemplified in the specification. Applicant's strategy for treating the claimed disorders and diseases is fraught with inaccuracies and that these methods are still notably deficient in defining and describing the complexity of sCD164 function in the inhibition of the proliferation of MBP specific T cells activated by Ac1-11 peptide in MS.

On the basis of the disclosed apparent *in vitro* observation alone, applicant concludes that the scope of the soluble protein defined by sequence encompassed by the claimed invention can have biological activity to treat inflammatory and/or autoimmune diseases such as multiple sclerosis (MS) and be provided as pharmaceutical compositions to subjects including human to effectively treat MS.

The influence of a scientific theory should depend on its empirical and demonstrable aspects and not its underlying logic. Yet such empirical and demonstrable aspects of the claimed method of treating MS with the sf-CD164 are lacked in the instant specification. No working empirical data demonstrating that the sf-CD164 would treat or reduce the severity of MS is disclosed. The specification does not teach how to extrapolate data obtained from in a cell-based assay from MBP-specific antigen processing and presentation to the development of effective in vivo mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the sf-CD164 exemplified in the specification.

Claims 41-42 recite a method of inhibiting the expression of one or more cytokines such as TNF-α with the sCD164 molecule. Example 3, on page 56 of the specification discloses that at a high dose of sf-CD164, significantly inhibited LPS-induced TNF-α release by 38% (Fig. 4). However, Wiendl *et al* provides an overview of clinical studies that have failed or been abandoned in MS. TNFα antagonists which have led to negative effects in two studies (Lenercept, Infliximab) which led to the paradoxically increase disease activity, i.e. MS.

Further, Example 4, on page 57 does not provide the skilled artisan with guidance for how to use the claimed sCD164 in a method of treating any inflammatory and/or autoimmune diseases such as MS. LPS induced peritoneal recruitment of neutrophils and lymphocytes in response to a nonspecific inflammatory stimulus. However, the skilled artisan would conclude that a positive result in this assay indicates that the sCD164 is capable of inhibiting inflammation in gerenal. This information does not guide the skilled artisan as to how to use the claimed sCD164 in a method of treating any inflammatory/autoimmune conditions. The thioglicollated-induced leukocyte peritoneal recruitment assay and LPS-induced peritoneal recruitment of neutrophils and lymphocytes are not a model of a specific human disease, it is a standard test for examination of interventions impacting on the adaptive immune system in vivo. sCD164 administration inhibited the cellular accumulation, it only confirms the role of CD164 in inflammation in general but not specific for any inflammatory/autoimmune diseases such as MS.

The art acknowledges that function cannot be predicted based solely on structural similarity to a

protein found in the sequence databases and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Attwood (Science 2000; 290:471-473, IDS ref. AR) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. There is tremendous variability in the importance of individual amino acids in protein sequences. Since the *O*-linked glycans of CD164 is a key determinant its MBP specific T cells proliferative activity, residue substitutions can have severe phenotypic effects. There is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. CD164 has the common characteristic of being highly glycosylated polypeptides, containing both O- and N-linked carbohydrate side chains. Monoclonal antibodies against CD164 that alter the adhesive and proliferative properties of hematopoietic precursors recognize epitopes that are destroyed by treatment of cells with sialidase, which cleaves terminal sialic acid residues on O- or N-linked carbohydrates, or *O*-sialoglycoprotease, an enzyme that selectively degrades *O*-sialomucins (see Lee et al IDS ref.). It would be predicted, therefore, that amino acid substitutions in the soluble CD164 molecule would effect CD164 MBP specific T cells functional activity. Importantly, ZANNETTINO (IDS *ref.)* teaches that the function of CD164 is not known. Zannettino et al (IDS ref) teach that murine MGC-24v and rat endolyn share significant sequence similarities with human CD164. However, CD164 lacks the consensus glycosaminoglycan (GAG)-attachment site found in MGC-24 (see page 2625, 1st col., top ¶). The specification fails to provide guidance on the importance of the GAG motif modification in the treatment of inflammation/autoimmune diseases. While the specification identifies some broad categories of CD164 molecules that *might* work, these descriptions, without more precise guidelines amount to little more than, "a starting point, a direction for further research." *Genentec, Inc. V. Novo Nordisk* A/S, 108 F.3d 1361, 1366, 42 U.S. PQ.2d (BNA) 1001, 1005 (Fed. Cir. 1997). Thus the recitation of percent identity language does not allow the skilled artisan to make and use the soluble protein of CD164 commensurate in scope with the instant claims without undue experimentation.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. Claims 24-26, 28-42 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an in vitro method of inhibiting the proliferation of MBP specific T cells induced by AC1-11 comprising contacting said cells with soluble CD164 polypeptide.

Applicant is not in possession of a method of treating any "inflammatory and/or autoimmune diseases" comprising the administration of a composition comprising a soluble protein

comprising sequence having at least "85% of homology with the mature form of the extracellular domain of human CD164 (SEQ ID NO:1)" in claim 24, wherein said soluble protein is an "active mutein or an isoform of SEQ ID NO: 1" in claim 26, wherein said soluble protein is an "active derivative, a proteolysis-resistant modified form, a conjugate, a complex, a traction, a precursor, and/or a salt" in claim 39, wherein said inflammatory and/or autoimmune disease is multiple sclerosis in claims 40 and 44, or a method of inhibiting the expression of one or more cytokines in an individual comprising administering to said individual a composition comprising a soluble protein comprising a sequence having "at least 85% of homology with the mature form of the extracellular domain of human CD 164 (SEQ ID NO: 1)" in claim 41, wherein said cytokine is TNF-α, IFN-γ, IL,-2, IL-4, II,-5, or IL-10.

Applicant has disclosed only amino acid of SEQ ID NOs: 1, 2, 4-6; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 15, 2007

Maher Haddad

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